Remarks

The Office Action mailed January 8, 2001, has been received and reviewed. Claims 1 through 12 and 14 through 21 are currently pending in the application, and each of claims 1 through 12 and 14 through 21 stand finally rejected. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. Priority Claim

Transmitted herewith is a certified copy of EP 97201440.1, thus perfecting the priority claim.

2. 35 U.S.C. § 102(b) Rejections

Claims 1 through 12, 14, 15, and 17 through 21 stand finally rejected as being anticipated by Tkachuk et al. Applicants respectfully traverse the rejection.

Tkachuk et al. provides a probe ("PEM12") that spans / overlaps the breakpoint cluster region (Tkachuk et al., p. 560, FIG. 1, lines 17-19). A second probe (*i.e.*, c-H-abl) is also provided by Tkachuk et al., separated from the first probe which spans / overlaps the breakpoint cluster region by a distance of between 15-200 base pairs (*Id.*, p. 560, Figure 1, lines 23-24). These probes are in stark contrast to the presently claimed invention where probes are provided which lie adjacent to or flank the breakpoint cluster region (*e.g.*, equidistant to the breakpoint region) and do not lie within or span or overlap the breakpoint cluster region.

Applicants specifically disclose that false positive diagnosis may arise from the a) the use of probes (such as the probes of Tkachuk) that overlap the breakpoint cluster region, and b) the use of probes (such as the probes of Tkachuk) directed against different chromosomes with juxtaposition of both signals into <u>one signal</u> in the case of translocation (Tkachuk, p. 560, Figures 1 & 2). In contrast, the claimed invention provides a means to avoid such false positive diagnoses by using the claimed probes, *i.e.*, ones lying adjacent to / flanking, but not lying within the breakpoint cluster region on one chromosome giving rise to a split signal (*i.e.*, <u>two separate signals</u>) after translocation. Accordingly, claims 1 through 12, 14, 15 and 17 through 21 are not anticipated.

Claim 16 was also finally rejected in the Office Action under Section 102(b), as assertedly being anticipated by Rowley et al. The kits disclosed by Rowley et al., however, do not provide

pairs of probes. The particular nucleic acid probes specified by Rowley et al. MLL 0.7B (SEQ.ID No 1:749 bp) and MLL 0.3BE (SEQ ID No 2: 343 bp) lie adjacent to one another and are smaller than 1 kb. Furthermore, MLL 0.7b lies within the breakpoint region (*see*, Figure 2). Due to their small size, such probes could not be used in combination with MLL 1.5 EB (1.420 kb) for FISH detection purposes. Accordingly, Rowely et al. cannot anticipate claim 16.

3. 35 U.S.C. § 112 , Second Paragraph, Rejections

The claims stand rejected under 35 U.S.C. § 112, second paragraph for use of the term "distinct". Applicants have amended the claims to remove the terminology, and, in view of the amendments, respectfully request that the rejection be withdrawn. Since these amendments remove issues for appeal, they should be entered.

Conclusion

Claims 1 through 12 and 14 through 21are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Office determine that additional issues remain which might be resolved by a telephone conference, the Examiner is respectfully invited to contact applicants' undersigned attorney.

Respectfully submitted,

Allen C. Turner
Registration No. 33,041
Attorney for Applicants
TRASK BRITT, PC
P. O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: (801) 532-1922

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CLAIMS WITH AMENDMENTS SHOWN

1. (Three times amended) A pair of [distinct] nucleic acid probes having comparable size, said size being selected from the group consisting of from 1 to 100 kb, from 1 to 10 kb, 7 to 15 kb, 10 to 20 kb, 10 to 30 kb, 20 to 40 kb, 30 to 50 kb, 40 to 60 kb, 50 to 70 kb, 60 to 80 kb, 70 to 90 kb, and 80 to 100 kb, and flanking a potential breakpoint in a chromosome, each of said pair of [distinct] probes being labelled with at least one different reporter molecule.

2. (Three times amended) A pair of [distinct] nucleic acid probes of comparable size, said size being selected from the group consisting of from 1 to 100 kb, from 1 to 10 kb, 7 to 15 kb, 10 to 20 kb, 10 to 30 kb, 20 to 40 kb, 30 to 50 kb, 40 to 60 kb, 50 to 70 kb, 60 to 80 kb, 70 to 90 kb, and 80 to 100 kb, and flanking a potential breakpoint in a chromosome, which pair of [distinct] nucleic acid probes hybridize to a nucleic acid molecule at a genomic distance of from about 50 kb to no more than 100 kb.

3. (Three times amended) The pair of [distinct] nucleic acid probes of comparable size of claim 1, which pair of [distinct] nucleic acid probes hybridize to a nucleic acid molecule at a genomic distance of from about 50 kb to no more than 100 kb.

4. (Three times amended) The pair of [distinct] nucleic acid probes of claim 2, each of said pair of [distinct] nucleic acid probes being labelled directly or indirectly with at least one reporter molecule.

5. (Three times amended) The pair of [distinct] nucleic acid probes of claim 4 wherein the at least one reporter molecule is selected from the group consisting of enzymes, chromophores, fluorochromes, and haptens.

6. (Three times amended) The pair of [distinct] nucleic acid probes of claim 5 wherein the probes hybridize to a single corresponding nucleic acid molecule.

7. (Three times amended) The pair of [distinct] nucleic acid probes of claim 6 wherein the single corresponding nucleic acid molecule is at least a fragment of a chromosome.

8. (Three times amended) The pair of [distinct] nucleic acid probes of claim 7 wherein the chromosome is not aberrant.

9. (Three times amended) The pair of [distinct] nucleic acid probes of claim 1 which hybridize *in situ*.

10. (Three times amended) The pair of [distinct] nucleic acid probes of claim 9, which pair of [distinct] probes each hybridize *in situ* to only a few linear DNA molecules per cell.

11. (Three times amended) A method of detecting a nucleic acid molecule having a chromosomal aberration, said method comprising:

providing a pair of [distinct] nucleic acid probes to analyze a sample believed to contain said nucleic acid, said [distinct] nucleic acid probes having comparable size, said size being selected from the group consisting of 1 to 100 kb, 1 to 10 kb, 7 to 15 kb, 10 to 20 kb, 10 to 30 kb, 20 to 40 kb, 30 to 50 kb, 40 to 60 kb, 50 to 70 kb, 60 to 80 kb, 70 to 90 kb and 80 to 100 kb, and said [distinct] nucleic acid probes flanking a potential breakpoint in a chromosome, each of said pair of [distinct] probes being labeled with at least one different reporter molecule;

hybridizing said [distinct] nucleic acid probes to said nucleic acid; and

detecting the presence of said reporter molecule.

12. (Three Times amended) A method of detecting cells suspected of having a chromosomal aberration, said method comprising:

providing a pair of [distinct] nucleic acid probes to analyze nucleic acid of said cells, said [distinct] nucleic acid probes having comparable size, said size being selected from the group consisting of 1 to 100 kb, 1 to 10 kb, 7 to 15 kb, 10 to 20 kb, 10 to 30 kb, 20 to 40 kb, 30 to 50 kb, 40 to 60 kb, 50 to 70 kb, 60 to 80 kb, 70 to 90 kb and 80 to 100 kb, and said [distinct] nucleic acid probes flanking a potential breakpoint in a chromosome, each of said pair of [distinct] probes being labeled with at least one different reporter molecule;

hybridizing said [distinct] nucleic acid probes to the nucleic acid of at least one of said cells; and

detecting the presence of said reporter molecule.

17. (Twice amended) The pair of [distinct] nucleic acid probes of claim 1 wherein the probes hybridize to a single corresponding nucleic acid molecule.

18. (Twice amended) The pair of [distinct] nucleic acid probes of claim 17 wherein the single corresponding nucleic acid molecule is at least a fragment of a chromosome.

19. (Twice amended) The pair of [distinct] nucleic acid probes of claim 18 wherein the chromosome is not aberrant

20. (Twice amended) The pair of [distinct] nucleic acid probes of claim 3 wherein the probes hybridize to a single corresponding nucleic acid molecule.

21. (Twice amended) The pair of [distinct] nucleic acid probes of claim 20 wherein the single corresponding nucleic acid molecule is at least a fragment of a chromosome.